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Acute and Recurrent Hepatitis Induced by 2,2-Dichloro-1,1,1-trifluoroethane (HCFC-123)

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Abstract: Acute and Recurrent Hepatitis Induced by 2,2-Dichloro-1,1,1-trifluoroethane (HCFC-123): Kazuyuki OMAE, et al. Department of Preventive Medicine and Public Health, School of Medicine, Keio University—A 49-yr-old female cleaning worker first visited a hospital because of acute hepatitis. On admission, laboratory examination revealed severe hepatic damage (AST 2125 IU/L, ALT 2391 IU/L, LDH 1279 IU/L, t-Bil 8.5 mg/dl), but failed to disclose any evidence of viral infection or morphological lesions. She recovered day by day without any specific treatment for hepatitis and was discharged one month later. On the 11th day after restarting her job, she was readmitted due to similar symptoms and signs. Serum biochemistry data again showed severe liver damage (AST 1354, ALT 1604, LDH 1119 t-Bil 2.6). Histopathological diagnosis based on hepatic needle biopsy was chronic active hepatitis with diffuse infiltration of lymphocyte-dominant inflammatory cells, bridging necrosis, intercellular fibrosis in a limited region, and with ballooning, degeneration, and/or necrosis of the hepatic cells. A job-related cause was suspected and 2,2-dichloro-1,1,1-trifluoroethane (HCFC-123), which has been proven to cause acute hepatitis in humans, was detected in a dry-cleaning solvent by gas chromatography-mass spectrometry analysis. A job simulation experiment suggested that the concentration of the patient’s exposure to HCFC-123 exceeded 1,000 ppm during the busiest work period, which was sufficiently high to induce severe liver damage.

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Intensive toxicological studies of eight alternative chemicals of fully halogenated chlorofluorocarbons, namely, difluoromethane, pentafluoroethane, 1,1,2,2-tetrafluoroethane, 2,2-dichloro-1,1,1-trifluoroethane (HCFC-123), 2-chloro-1,1,1,2-tetrafluoroethane (HCFC-124), 1,1-dichloro-1-fluoroethane (HCFC-141b), and two isomers of dichloropentafluoropropane, were performed by the Programme for Alternative Fluorocarbon Toxicity Testing (PAFT) sponsored by 16 of the world’s leading fluorocarbon producers¹. Because the results of single-to-2-yr exposure experiments with these alternatives showed minimal health effects on rats and dogs including effects on the liver, they were marketed as substances which were relatively less toxic and less ozone-depleting.

In the middle of June, 1999, a female patient experienced recurring acute hepatitis and a physician in internal medicine suspected that the cause might be work-related. The causal agent was suspected to be cleaning solvent used in her work site containing 80% of HCFC-141b and 20% n-heptane.

Case report

A 49-yr-old woman who was an occasional drinker and who had no history of blood transfusion, liver diseases, alcohol-related disorder, or habitual use of medicines, and who worked as a cleaner in the bridal section of a hotel, first noticed a darkening of her urine in early March, 1999, and felt abdominal unpleasantness, nausea, and had yellowish sclera around March 10. She went to a hospital on March 17 and detailed clinical and laboratory examinations were conducted. Her serum hepatic function parameters were extremely high: aspartate aminotransferase (AST) 2125 IU/L, alanine
aminotransferase (ALT) 2391 IU/L, alkali phosphatase (ALP) 217 IU/L, gamma-glutamyltranspeptidase (GGT) 294 IU/L, lactate dehydrogenase (LDH) 1279 IU/L, and total bilirubin (t-Bil) 8.5 mg/dL. Clinical diagnosis was acute hepatitis of unknown etiology, and she was admitted to the hospital on that day.

Antigen and/or antibody of hepatitis A virus, hepatitis B virus and hepatitis C virus were all negative. IgG anti-EB virus capsid antigen (EB-VCA) and IgG anti-EB virus nuclear antigen were positive but IgM anti-EB-VCA was negative, which indicated she had a past history of EB virus infection. IgG anti-cytomegalovirus (CMV) was positive but her IgM anti-CMV was negative, which ruled out recent CMV infection. Both abdominal CT and echogram indicated only secondary thickening of the gall bladder wall.

The serum parameters of hepatic function and clinical conditions improved day by day without specific treatment for hepatitis except for bed rest and general liver supporting therapy (Fig. 1). Results of the last serum examinations on April 20 were: AST 31, ALT 55, ALP 97, GGT 82, LDH 236 and t-Bil 1.2, and she was discharged on the next day.

She restarted her job on the first day of May. At that night, her body temperature rose 38°C. Due to the occurrence of similar subjective symptoms and objective signs to those on her first admission, she was readmitted to the same hospital on May 11. Her serum chemistry data were: AST 1354, ALT 1604, ALP 200, GGT 193, LDH 1119 and t-Bil 2.6. Hepatitis G virus RNA was negative. Abdominal CT and echogram detected no lesions. Hepatic needle biopsy was conducted on May 17. Histopathological diagnosis was chronic active hepatitis with diffuse infiltration of lymphocyte-dominant inflammatory cells in both the portal and lobular areas, bridging necrosis and intercellular fibrosis in limited regions, and with ballooning, degeneration and/or necrosis of the hepatic cells. A pathologist suggested the possibility of an autoimmune hepatitis, but tests for autoimmune diseases, namely, anti-nuclear antibody, anti-mitochondria antibody, and anti-RNP antibody, were all negative.

The clinical course of the second admission was the similar to the first. About one month later, the serum levels of liver dysfunction parameters improved: AST 31, ALT 32, ALP 93, GGT 57, LDH 261, and t-Bil 1.1.

**Job history**

She had worked as a dry cleaner of ceremonial dresses for 8 yr. During the first 6 yr, 1,1,1-trichloroethane was a major component of cleaning solvent until it was banned due to its strong ozone depleting potential in 1996. The alternative cleaning solvent contained 80% of HCFC-141b and 20% of n-heptane according to the information provided by the company supplying the solvent (Fujibright G-1, Solvex Co.). In October 1998, her working place was moved to a smaller room with a small exhaust fan that was insufficient for solvent vapor elimination (Fig. 2). There was a window in her workplace, but it was not opened.

She held a ceremonial dress with her left hand without protective gloves or mask, applied the cleaning solvent to dirty and stained areas of the dress with a handy-type spray gun, and hung it on the rack in the room to vaporize the solvent. The solvent which spilled onto towels and clothes on a dry-cleaning bench also evaporated into the room. In the bridal season, she worked about one hr a day at the dry cleaning job, and stayed in the room for other jobs.

She left the job after her second discharge from hospital.

**Analysis of the solvent components**

Components of the cleaning solvent were analyzed by gas chromatography with a mass spectrometer as a detector (GC-MS, G1800B GCD system, Hewlett
Packard Co.) equipped with an automatic sample injector (HP 6890 Series Injector, Hewlett Packard Co.) and a data-acquisition and processing system (HP Vector XV computer with the HP Chemistation software, Hewlett Packard Co.). A capillary column HP-1 (30 m length, 0.25 mm in diameter, 1 µm film thickness, Hewlett Packard Co.) was employed. The injection port was heated to 250°C and the transfer line to 300°C. The carrier gas was helium with a flow rate of 1 ml/min. Column temperature was kept at 40°C.

As shown in Fig. 3, four major peaks were detected. Based on information from the mass spectrometry data library, agents of the peaks were identified as water (retention time 1.28 min), HCFC-123 (2.05), HCFC-141b (2.25), and n-heptane (8.58). Chromatographic peaks of HCFC-123 with 99.5% purity (Asahi Glass Co.), HCFC-141b with >99% purity (Central Chemicals Co.), and n-heptane (Special grade, Wako Pure Chemicals Co.) had the same retention time as the three peaks of the solvent, which reconfirmed that the three peaks were HCFC-123, HCFC-141b, and n-heptane. Quantitative analysis showed that the solvent consisted of 23.7% (mol/mol) of HCFC-123, 29.7% of HCFC-141b, and 46.4% of n-heptane, respectively.

**Estimation of exposure concentration**

Based on the patient’s detailed description of her job conditions, exposure concentrations during the busiest working period, namely, repetitions of 10 min of cleaning with a 5 min rest for 1.5 hr, were estimated by performing an experimental job simulation in the cleaning room. One of the authors (Subject X) simulated the job by using the same cleaning solvent and spray gun. Another author (Subject Y) conducted air sampling during and after the simulation. They wore respiratory protective devices (Chemical cartridge GH800S, Sanko Chemical Ind.) and attached air sampling tubes containing 400 mg activated charcoal absorbent (Jumbo Type; Shibata Scientific Technology, Ltd.) to their collar to assess the amount of solvent concentration each of them was exposed to. Room air was collected above a dry-cleaning bench (Point A) and in front of a wardrobe (Point B) 1.3 m above the floor with the same sampling tubes (Fig. 2). One hundred ml/min of air was sampled for 10 min with an air suction pump (PMP-05D, Shibata Scientific Technology, Ltd.), and the sampling tube was changed at 10 min intervals.

The activated charcoal absorbent was desorbed with 2 ml dichloromethane, and 1 µL of the adsorbent was directly injected into the GC-MS system. Concentrations of HCFC-123, HCFC-141b, and n-heptane were determined by the signals of selected ion fragments at 83 m/z, 81 m/z, and 43 m/z by a selected ion method mode. Average exposure concentrations of HCFC-123, HCFC-141b, and n-heptane during the job simulation were 1,367, 2,047, and 3,457 ppm in Subject X and 1,591, 2,307, and 2,676 ppm in Subject Y. Geometric mean concentrations during the simulation were 1,355, 1,901, and 1,814 ppm at point A, and 1,986, 2,778, and 2,626 ppm at point B, and gradually decreased after completing the job simulation. Room temperature was 23.5°C at the
beginning of the simulation and 19.0°C at the end of it probably due to heat loss caused by solvent evaporation.

**Discussion**

Comprehensive clinical and laboratory examinations could not identify the cause of the patient’s recurrent hepatitis. Job-related factors were suspected and the dry-cleaning solvent was focused on as a causal agent because of the coherent temporal relationships between its use in a smaller working room and the first onset of the hepatitis, and between restarting the job and recurrence of the hepatitis, but HCFC-141b and n-heptane, the components of the solvent according to the supplier, were unlikely to induce acute severe hepatitis.

The results of intensive rat and rabbit exposure experiments with HCFC-141b by PAFT indicated low inhalation toxicity in acute, subchronic\textsuperscript{2)}, and chronic\textsuperscript{3)} inhalation experiments, no genotoxic potential\textsuperscript{3)}, and no teratogenic or reproductive toxicity\textsuperscript{4)}. Its major and minor metabolites in humans were 2,2-dichloro-2-fluoroethyl glucuronide and 2,2-dichloro-2-fluoroacetic acid\textsuperscript{5)}, both of which were also detected in animal experiments\textsuperscript{6)}, indicating that the main metabolic pathway of HCFC-141b in humans is the same as in rats. No covalent binding of fluorinated metabolites of HCFC-141b to liver proteins was detected\textsuperscript{6)}, suggesting that hepatotoxic intermediates are not produced in the process of HCFC-141b biotransformation. Consequently, it is unlikely that HCFC-141b is a cause of human acute hepatitis. n-Heptane is also unlikely to cause human acute hepatitis\textsuperscript{7)}.

On the other hand, HCFC-123, which was unexpectedly disclosed as one of the components of the cleaning solvent, has been proven to be a human hepatotoxic chemical, even though the results of PAFT experiments showed low toxicity of HCFC-123 in rats and dogs. Hoet et al.\textsuperscript{8)} first reported an epidemic of liver dysfunction among workers accidentally and repeatedly exposed to a mixture of HCFC-123 and HCFC-124 leaked from pinholes of an air conditioning pipe in 1997. Takebayashi et al.\textsuperscript{9,10)} ascertained that HCFC-123 was a single causal agent of human hepatic injury in an exposure-effect and exposure-response manner based on the incident of acute hepatitis and liver dysfunction observed in 14 HCFC-123-exposed workers without any exposure to other hazardous substances. They indicated that severe liver dysfunction in humans could be induced when repeated exposure to HCFC-123 exceeded 200 ppm with peak concentrations above 1,000 ppm during no more than five weeks. In the present case, it may be without doubt that she was working with sufficiently high and long-term exposure to HCFC-123 to induce liver damage based on the results of the simulation experiment and her job history.

In conclusion, HCFC-123 may be the cause of the recurrent hepatitis in this case, even though objective evidence of HCFC-123 exposure, such as metabolite determination in urine\textsuperscript{11)} or metabolite-protein complex in the liver cells\textsuperscript{8)}, could not be obtained.

**References**